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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/005,793	11/02/2001	Jacobus Christianus Johannes Stiekema	O/97277 US/D1	3402

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EXAMINER	
EBRAHIM, NABILA G	
ART UNIT	**PAPER NUMBER**
1618	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/005,793	JOHANNES STIEKEMA ET AL.	
	Examiner	Art Unit	
	Nabila G. Ebrahim	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 1/7/2005.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 11-26 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) 11-26 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt of amendment filed 7/8/2004 is acknowledged.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11-26 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention in preventing the clotting induced by contact with surfaces in an extracorporeal blood circuit for a patient undergoing chronic, intermittent, extracorporeal blood treatment.

a) The term preventive is all-inclusive, no exceptions, no conditions, it is very broad. Nature of invention is preventing coagulation from occurring by the use of a pharmaceutical formulation enterally, parenterally or in an extracorporeal blood circuit in patients undergoing chronic, intermittent, extracorporeal blood treatment.

b) State of art teaches reducing the risk but not preventing, see patents US 6183743, US 6180625, US 6166064, and US 6166168.

c) Level of ordinary skill is high given the subject matter of preventing the occurrence of a condition.

d) Predictability in the art would be that one can reduce the risk or treat but not prevent.

e) Direction provided shows the treating but insufficient data has been presented and establish the ability to prevent.

f) The instant application show one working example for preventing, the example is done using only one compound (Org 31540/SR 90107 A), done for minimal number of population (12 patients), one way of administration was used (intravenous bolus), and data was collected only twice on the dialysis day and only for three days post-dialysis. This one trial does not provide sufficient reliable results to achieve the prevention objective.

g) Quantity of experimentation is high for the theory of the ability to prevent and must take in consideration a multitude of factors including: age, pathogenic factor, gender, lifestyle, habits, familial tendency, etc.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the

> prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 11-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kudo et al. U.S. patent 4,331,697, in view of Ahmad et al. U.S. 5,252,213, and further in view of Petitou et al. U.S. 5,378,829.

Kudo et al. teaches that biomedical materials, such as extracorporeal blood circuits which make direct contact with the blood, are used to temporarily conduct the blood out of the body or for substituting body organs with artificial organs. (col. 1, lines 19-30). Kudo et al. teaches also that when upon blood contact with the surfaces of these devices it coagulates and forms a thrombus on their surfaces, which can stop the blood flow or moves with blood to cause serious complications (col. 1, lines 19-30). Kudo et al teaches that to suppress

the risk of forming these thrombi, it is recommended to administer an antithrombotic agent, such as heparin, coumarine, or sodium citrate (col.1, line 41 to col. 2, line 51). Thus, Kudo et al. provides the general teachings that extracorporeal circuits cause blood clotting upon contact with the blood of a patient and the blood clotting is prevented by the administration of an anticoagulant agent. Kudo et al. is deficient in the sense, that it does not specify compounds claimed in the instant application among the antithrombotic agents used in the invention.

Ahmad et al. teaches that hemodialysis treatment is used as a therapeutic measure when a patient's kidneys no longer perform their blood purifying function because of disease or traumatic removal and most kidney failure patients require dialysis treatment three times weekly (See col. 1, lines 44-60). Ahmad et al. teaches that the contemporary dialysis machine has a blood circuit comprising a blood pump, and during treatment, blood is drawn from the patient, pumped into the hemodialyzer and returned to the patient (See col. 3, lines 20-26) Additionally, Ahmad et al. teaches that the dialysis machine comprises a means for adding an anticoagulant to the blood circuit to minimize fibrin ring deposits, and includes heparin fragments among the anticoagulants used in the invention (See col. 5, line 59 to col. 6, line 10).

Thus, Ahmad et al. teaches that patients suffering from renal failure undergo chronic, intermittent extracorporeal blood circuit treatment, and thrombus formation in dialysis machines is prevented by the addition of anticoagulant agents, such as heparin derivatives.

Petitou et al. discloses sulfated glycosaminoglycanoid derivatives of heparin, and the pentasaccharides claimed in claims 11 -18 of the instant application among them, and teaches that the compounds have antithrombin and antithrombotic activity, a better pharmacokinetic profile, longer half-life times, lower therapeutic doses and thus lesser side-effects (col. 1 lines 37-40), and can be administered enterally or parenterally, including by injection, in a daily dosage of 0.001-10 mg. per kg. body weight (col. 1, line 1 to col. 5, line 5 and examples). The daily dosage disclosed by the prior art is identical to the dosage per treatment claimed by Applicant in claims 11 and 15 of the instant application, and it is in the dosage range claimed by applicant in claims 12 and 16 of the application. Therefore, in the absence of unexpected results, it would have been obvious to one having ordinary skill in the art at the time the invention was made to apply the teachings of Kudo et al. and Ahmad et al. to device a method for preventing clotting induced by contact of extracorporeal circuit surfaces with the blood of a patient comprising administering to the patient undergoing extracorporeal blood treatment or to the circuit anticoagulant agents, and include the sulfated glycosaminoglycanoid derivatives of heparin disclosed by Petitou et al., as anticoagulant agents motivated by the facts that it has better pharmacokinetic profile, longer half-life times, and lower therapeutic doses and thus lesser side-effects. The expected result would have been a successful method for preventing blood clotting in extracorporeal circuits, which would otherwise lead to complications in the patient undergoing extracorporeal blood circuit treatment.

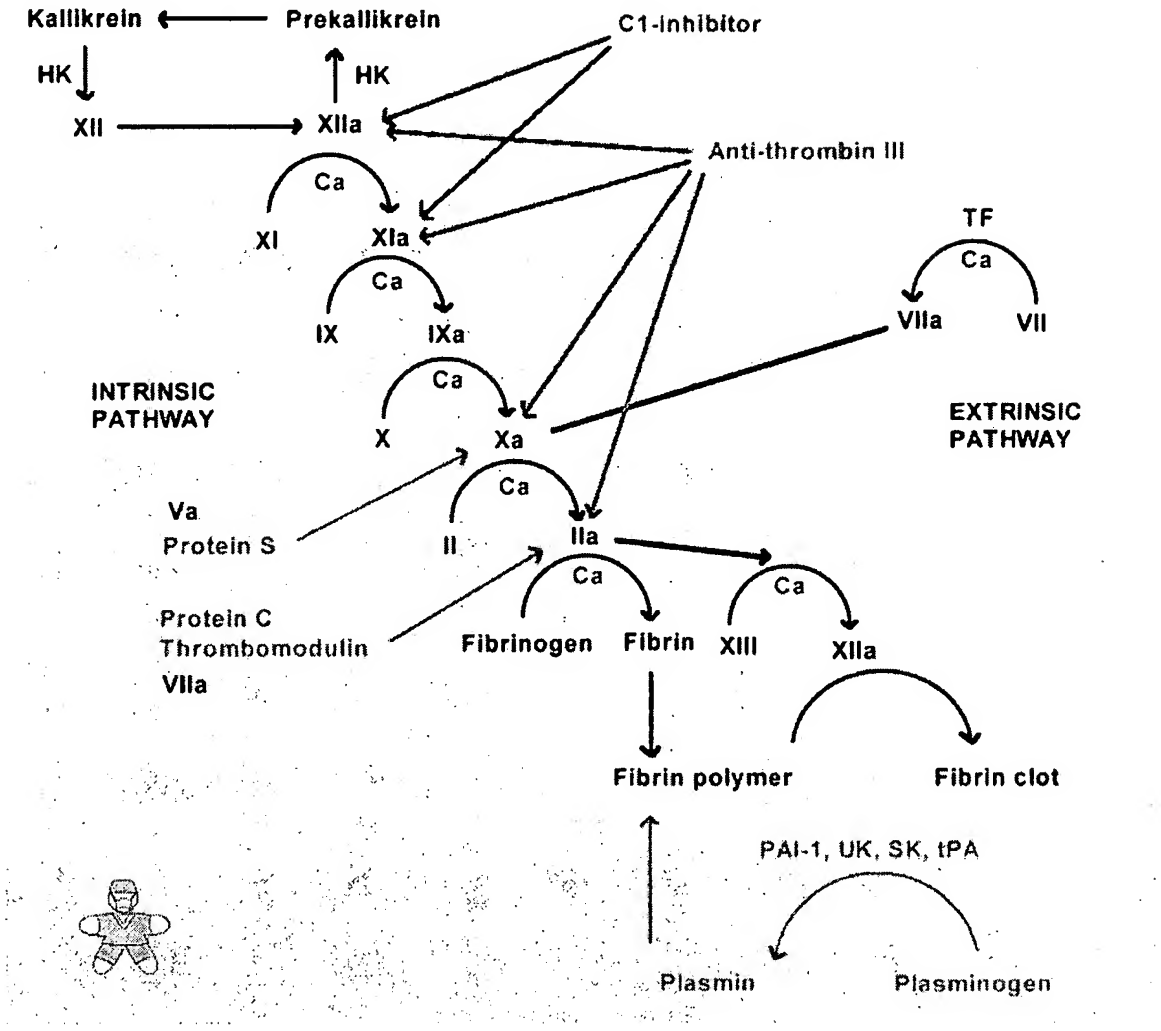
Response to Arguments

Applicant's arguments filed 7/8/2004 have been fully considered but they are not persuasive. Applicant traverses the previous rejections by arguing that:

- The synthetic oligosaccharides of the instant application are highly and selectively inhibit factor Xa via anti-thrombin III, yet have no activity on thrombin.
- Kudo et al. does not teach or suggest the use of any synthetic oligosaccharides, to prevent clotting in an extracorporeal blood circuit, describe intermittent extracorporeal blood treatment, or teach the required dosage of any antithrombotic agent, which would prevent clotting in an extracorporeal blood circuit.
- Ahmed et al. does not teach or suggest administration of an anticoagulant to a patient undergoing intermittent treatment, and do not teach or suggest the use of the oligosaccharides of the instant invention in preventing thrombus formation in dialysis machines or suggest the dosage required for any anticoagulant that would result in such prevention.
- Petitou et al. describes compounds taught to be useful as thrombus generation inhibitors and as inhibitors of smooth muscle cell proliferation. The applicant also argues the dose Petitou et al. disclosed in his invention claiming that the dose is given for treatment of venous thrombosis or for the inhibition of smooth muscle proliferation, not for extracorporeal blood circuit, so he fails to teach the necessary dosage for such use.

In response to the above argument, the examiner position is to confirm that claims 11-18 have been appropriately rejected under 103(a) as being unpatentable over Kudo et al. U.S. patent 4,331,697, in view of Ahmad et al. U.S. 5,252,213, and further in view of Petitou et al. U.S. 5,378,829.

Kudo et al. is teaching a method for imparting antithrombotic activity to a biomedical material, which comprises treating that surface of the biomedical material, which makes contact with the blood with a heparin derivative (claim). Though this method does not teach the use of oligosacchardes, it uses the same mechanism of interrupting the clotting cascade by interrupting thrombin activation through Antithrombin III, which is the most important thrombin regulator, since it can also inhibit the activities of factors IXa, Xa, XIa and XIIa. The activity of antithrombin III is potentiated in the presence of heparin. This effect of heparin is the basis for its clinical use as an anticoagulant. This is considered the parent idea for using anticoagulants in extracorporeal blood circuits, and on its teaching part of the instant application is based (specification page 3, lines 9,10).



http://www.surgicaltutor.org.uk/defaulthome.htm?core/preop2/clotting.htm~right

The diagram shows the clotting cascade and clearly shows antithrombin III and how it controls many clotting factors, if any of these factors are interrupted at any point the result will be reduction of the risk of blood coagulation.

Ahmed et al. invention was directed to modifying automated hemodialysis-filtration system that enables monitoring of the patient and adjustments of the dialysis system according to the changing needs of the patient without the constant vigilance of an assistant. Though it did not relate directly to reducing the risk of blood clotting in an extracorporeal blood circuit, it disclosed the using of

anticoagulants in the drip chamber, and gave examples of anticoagulants, as heparin, heparin fragments, ...etc, (col. 6, lines 7-10) which does not include oligosaccharides but these examples are only considered representative and not inclusive in the usage of anticoagulants in his invention.

The compounds of Petitou et al. are used as thrombus generation inhibitors (col. 1, lines 44,45) in a dosage of 0.001 to 10 mg/kg for the treatment of venous thrombosis due to their great antithrombin III binding affinity (col. 1, lines 35,36), since it is the antithrombin functions to inhibit several activated coagulation factors including thrombin, factor IXa and factor Xa, by forming a stable complex with the various factors, and it was disclosed that the compounds of Petitou et al. are effective in antithrombin III binding affinity, it is considered the same mechanism that the compounds of the instant application is using even though Petitou et al. did not disclose that it works through factor Xa.

These compounds are given enterally, or parenterally and are directed to inhibit thrombus formation in the blood regardless of the vessel (body vessel or extracorporeal vessel). It is expected that the effective dose that is used for this objective would be the same for the human blood in any vessel if directed to accomplish the same objective.

Obviousness is clear in regards of motivation by Petitou et al., there is no obviousness in trying but the motivation is clear in the teaching of the effect of the compound that is used for reducing the risk of or treating venous thrombosis and applying it in extracorporeal blood circuit, Petitou et al. discloses a better pharmacokinetic profile, longer half-life times, and lower therapeutic doses and

thus lesser side-effects (col. 1 lines 37-40), which is a strong motivation to an ordinary skilled man in the art to use the teaching of Petitou et al. combined with the teaching of Ahmad et al. with a reasonable expectation for success.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on 571-272-0602. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Nabila Ebrahim 7/7/2005

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